REMARKS

Claims 1-52 are pending in the application. The Applicants has amended independent Claims 1, 26, 30 and 49 to delete the word "spray-dried." Applicants realized that the term "spray-dried" was unnecessarily limiting and caused the Examiner confusion so the term, which was added by amendment dated 27 January 2003, has been removed. In addition, for clarity, Claim 30 has been amended to add the term "is capable of being delivered to the pulmonary system."

Claims Rejections under 35 USC § 102(e)

The Examiner has rejected Claims 1-7, 11-17, 21-26, 28, 49 and 51 are rejected under 35 USC § 102(e) as being anticipated by US Patent 6,043,214 to Jensen *et al.*

Applicants have deleted the term "spray-dried" as it was unnecessarily limiting and confused the Examiner. Accordingly the comments of the Examiner on Page 4 of the Office Action discussing the limitation of "spray drying" are rendered moot.

The Examiner has stated that "[a]ll that is required to anticipate Claim 1 is method of delivery to the pulmonary system of a powder comprising a multivalent cation, an active and a carrier." The Applicants respectfully disagrees.

Jensen is not enabling

In order to be prior art under 35 USC § 102(e), the reference *must teach* every element of the claims and it must be an *"enabled"* disclosure. A simple assertion by the Patentee that it performs one way or another is not enough. Further, picking and choosing by the Examiner of random ingredients listed in Jensen does not rise to the level of a teaching of the claimed method of delivering the powders as conceived of and reduced to practice by the Applicants. A more detailed discussion follows.

Jensen does not teach pulmonary delivery

In Claim 1, the powder of the instant invention must be administered to the pulmonary system and the agent released in a sustained manner.

The Examiner stated that Jensen teaches that administration of insulin via the pulmonary route can be accomplished by either an aqueous solution or a powder preparation (Col. 1, lines 51-55). Applicants respectfully point out that this section on which the Examiner depends for support is entitled "Description of the *Background Art.*" A closer look reveals that Col. 1, lines 51-55, support the assumption that it is the *prior art* the Jensen states is can be administered via the pulmonary route, not Jensen's own powders.

A closer reading of the Jensen specification reveals the Jensen deftly avoids all reference to pulmonary delivery, except for the aforementioned Background section and in his own definition of "enhancer." Yet, this definition is not a "teaching." The Patentee can be his own lexicographer and Jensen has done so with respect to the term "enhancer." The specification is devoid of any evidence that his so-called "enhancers" perform as defined. See Col. 2, lines 16-21, for the definition. There is not a shred of information showing that Jensen's powders reach the alveoli and certainly no evidence that the powders get absorbed across the alveoli. Jensen made powders but did not subject his powders to the rigors of any in vitro or in vivo experiments to demonstrate that the powders were either (1) capable of being delivered in a powder form to the lung, (2) absorbed by the lung or (3) therapeutic at all. Just because a powder contains insulin, does not make it therapeutic. At best, it appears that Jensen simply produced some insulin-containing powders which he looked at under a polarized light microscope. He did no more. As the Examiner can appreciate, delivery to the lung, especially a therapeutic amount, is not trivial and cannot be assumed. Hundreds of scientists are devoting themselves daily to this important endeavor trying to crack this difficult technology area. To credit Jensen with "pulmonary delivery" based upon this spare disclosure does an injustice to those toiling in the field.

Jensen does not teach sustained release

The Examiner has overlooked the fact that the Applicants' claim an essential feature that the "release must be sustained." As noted above, since no testing was performed with the Jensen powders, there is no teaching that the release is sustained.

Applicants do teach sustained release

In contrast the de minimus effort made by Jensen, the Applicants has produced dry powders, delivered pulmonarily the dried powders to rats in controlled experiments and compared the absorption with the standard therapy of commercially available insulin therapy. The rate and extent of insulin absorption into the blood stream after pulmonary administration of dry powders containing insulin to rats was determined. For comparison of insulin absorption with standard therapy, a commercially available insulin formulation, Humulin L, available from Eli Lilly and Co. was also tested in rats. Powder formulations with different insulin contents and varying amounts of total zinc were tested in order to determine the effect of varying formulations o the pharmacokinetic profile. See page 32, lines 9-15 as well as 32-35 of the specification.

Jensen powders do not have a median geometric diameter of about 5-30 μm

Although the Examiner does not list Claim 30 as being rejected under 35 USC § 102(e), The Examiner includes Claim 30 in her "Response to Arguments" on page 4 of the Office Action. Accordingly, Applicants are including a response to the Examiner's remarks for completeness.

Claim 30, as amended, is patentable based upon the suitability for pulmonary delivery of the composition of the instant invention. For the reasons stated above, Applicants believe that for this reason alone, Claim 30 is patentable. However, additional features of Claim 30 also patentably distinguish the instant invention from Jensen.

In Claim 30, Applicants claim features of their particles including tap density, median geometric diameter and aerodynamic diameter. Unfortunately, Jensen is silent as to tap density and aerodynamic diameter. The only feature which Applicants can correlate is the geometric diameter. The only reference to particle size in Jensen is in his Examples where Jensen discloses the size of "individual crystals" as determined by polarized light microscopy as being 1μm-5μm.

Example I	Col. 4, lines 46-37	Size of the individual crystals was determined to 1μm-5μm.
Example II	Col. 5, lines 8-9	Size of the individual crystals was determined to 1μm-5μm.
Example III	Col. 5, line 34	Size of the individual crystals was determined to 1μm-5μm.
Example IV	Col. 5, lines 62-62	Size of the individual crystals was determined to 1μm-5μm.

As can be seen, all of Jensen's' particles were determined to 1μm-5μm. One skilled in the art knows that the formation of particles generally fall into a particle distribution curves, as do the particles of the instant invention. Particle size distribution, as the term "distribution" is used in statistics, refers to the range within which the entire population falls. (*American Heritage Dictionary of the English Language,* Third Edition, Houghton Mifflin Company, 1992.) That is, all particles are not the same size rather there is a range of sizes. Claim 30 claims "median geometric diameter of from about 5 micrometers to about 30 micrometers." The median is defined as, the middle value in a distribution, above and below which lie an equal number of values. (*American Heritage Dictionary of the English Language, supra.)* From a statistical point of view, the 1-5μm individual crystals of Jensen cannot be the "about 5μm *median* geometric diameter" powders of Claim 30. Accordingly, the powders of Jensen do not describe or teach the powders of the instant invention.

For the reasons stated above, Applicants request that the Examiner's rejection of the claims based upon 35 USC § 102(e) be withdraw and that the claims, as amended, be allowed.

Claims Rejections under 35 USC § 103

The Examiner rejected Claims 1-52 based upon 35 USC § 103(a) as being unpatentable over Jensen *et al.* as discussed above for the rejections under 35 USC § 102(e). Thus, the arguments presented above are incorporated herein by reference and also apply to the rejections by the Examiner of Claims 1-52 based upon 35 USC § 103(a).

The Examiner has said that in the absence of evidence to the contrary, the burden is upon the applicant to prove that the claimed products are functionally different than those taught by the prior art and to establish patentable differences. As stated above, beyond a self-serving statement by the Patentee that his powders "enhance pulmonary delivery," Jensen does not teach

pulmonary delivery or powders capable of being pulmonarily delivered. One of the concerns of the Applicants is the aerodynamic properties of the powders of the instant invention. Such aerodynamic properties matter when one attempts to deliver a dry powder to the lung. A random selection of ingredients from the list in the Jensen disclosure does not teach a "formulation for pulmonary use." At best, Jensen teaches a method to precipitate particles composed of insulin and enhancer. See Jensen Col. 2, lines 36-40. Further, Jensen does not teach or suggest the combination of the ingredients or method of preparing the powders of the instant invention. One skilled in the relevant art seeking to prepare and deliver aerodynamically superior, sustained release powders would not look to Jensen's untested powders prepared by a two step precipitation then vacuum drying process. Such a process very likely produces very small and dense powders quite unlike the powders of the instant invention.

The Examiner admits that Jensen does not teach tap density. Applicants agree. As mentioned above, the powders of Jensen are very likely dense powders. Further, the only dimension that Applicants can discern, "individual crystal size" of 1-5 microns is significantly different from the median geometric diameter of the instant invention. Thus, one skilled in the art looking to prepare the powders having the properties of the instant invention would not look to Jensen for guidance.

The Examiner admits that Jensen does not teach the inclusion of carboxylic acid for pH adjustment but that one of ordinary skill in the art would be motivated to use it an expect a result of "a successful formulation for the pulmonary delivery of insulin." Wishing that it were so, does not make it so. Nothing in Jensen suggests that carboxylic acid should be selected over any other known ingredient especially for preparing powders capable for pulmonary delivery. Simply stated, a careful reading of Jensen reveals that Jensen prepared powders but did not actually deliver any, especially pulmonarily. Pulmonary delivery of insulin is not trivial. For the reasons stated above, the rejection must be withdrawn.

Information Disclosure Statement

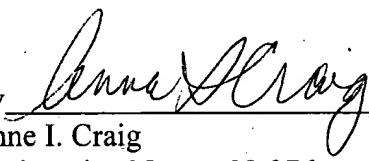
A second Supplemental Information Disclosure Statement (SIDS) was filed on April 9, 2003. Entry of the IDS is respectfully requested.

CONCLUSION

In view of the above amendments and remarks, Applicants believe that all the claims are in condition for allowance and a prompt notice to that effect would be greatly appreciated. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned.

Respectfully submitted,

ELMORE CRAIG, P.C.

By 

Anne I. Craig
Registration No: 32,976
Telephone: (978) 251-3509
Facsimile: (978) 251-3973

Dated: October 23, 2003